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Human Laboratory and Neuroimaging Studies in Substance Use Disorders: Developing New Treatment Approaches

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The *American Journal of Drug and Alcohol Abuse* has published numerous articles addressing psychosocial epidemiology and treatment outcome for substance use disorders, but relatively few studies involving neuroimaging or human laboratory studies. These types of studies help us to understand the pathophysiology of drug dependence and to efficiently test potential pharmacotherapies based on this understanding. Techniques such as neuroimaging directly show drugs' impact on the brain, and drug self-administration can induce the actual behaviors of addicted patients much more potently than visual, tactile, aural, or cognitive cues.

In this issue of the *American Journal of Drug and Alcohol Abuse* we include a new human neuroimaging technology for assessment of potential medication targets—neuroimaging using diffusion tensor imaging (DTI). This technique assesses both the structure and functional activity of the white matter axons and is less familiar to most readers than the more common neuroimaging of gray matter that includes neuronal and glial cell bodies. Neuroimaging of gray matter function is typically done through glucose utilization (FDG-PET), cerebral blood flow, magnetic resonance spectroscopy, or molecular imaging of receptor and transporter occupancy.

Moeller's article utilizes DTI to access the chronic effects of 3, 4-methylenedioxymethamphetamine (MDMA) use on human brain structure and the functional integrity of the axons connecting the gray matter regions of neuronal cell bodies. Previous studies using magnetic resonance spectroscopy to measure metabolic activity in the neuronal cell bodies and voxel based morphometry to measure the larger visible structure of both gray and white matter have shown mixed results when comparing MDMA users and nonusers. The promise of DTI is to provide information about microstructure of brain white matter organization, at which level structure and functional interact. The DTI assessed the axons the corpus callosum, which connects the two sides of the brain and is the largest white matter or axonal structure in the brain. In this

study, MDMA users and nonusers also were compared on measures of impulsivity and decision making using the Barratt Impulsiveness Scale and the Iowa Gambling Task (IGT). Axonal transmission, as measured by longitudinal diffusivities, were abnormal in the rostral part of the corpus callosum, which connects the frontal brain areas involved in decision-making and impulse control. A significant, positive correlation between more abnormal axonal function in the corpus callosum and disadvantageous choices on the IGT were shown. Thus, the brain areas involved in decision-making and impulse control were poorly interconnected in these MDMA suggesting that medications might improve impulse control if they can improve the ability to allow neurotransmission between these frontal brain areas—a significant area for medication development in many other de-mylinating brain diseases such as multiple sclerosis.

As we considered new medications, self-administration of abused substances such as cocaine or amphetamine in the human laboratory model can more precisely approximate the outcomes expected in the less controlled and inherently more risky outpatient testing of new medications. While medical safety considerations may limit the dosage given in the laboratory, this paradigm clearly approximates drug taking behavior in the outpatient setting. The laboratory also tests the effects a new medication might have in blocking or perhaps enhancing the reinforcing or adverse effects of abused drugs.

The Stoops article is an example of this human laboratory paradigm and examines effects of self-administered intranasal cocaine during maintenance on aripiprazole. Subjects received either aripiprazole or placebo in a cross-over design of two experimental sessions. Once the subject was maintained on the aripiprazole or placebo, four intranasal cocaine doses were given in ascending order, as is consistent with medical safety during self-administration studies. Physiological and subject-rated measures were evaluated. In this paradigm the key outcome of cocaine interactions with potential pharmacotherapies yields not only medical safety data, but also surrogate efficacy data through subjective responses to interactions between the medication and the abused drugs. These reactions might also indicate interactions that will discourage compliance with the medication. Overall, this is a powerful paradigm for medication development because of its potential to inform more expensive and perhaps risky clinical trials particularly if or when the patient takes their abused drug in combination with the medication. Its utility as a rapid screening procedure for eliminating medications from further outpatient testing has yet to be demonstrated for stimulant dependence, but these highly controlled paradigms have demonstrated efficacy in developing medications for other abused drugs and for testing abuse liability of new medications.

We therefore hope our readership can enjoy the challenges of these somewhat uncommon types of articles for the *American Journal of Drug and Alcohol Abuse* and we will hope to publish more of them in the future.